METHODS FOR THE FORMULATION AND MANUFACTURE OF ARTESUNIC ACID FOR INJECTION

GOVERNMENT INTEREST

[0001] The invention described herein may be manufactured, used and licensed by or for the U.S. Government.

BACKGROUND OF THE. INVENTION

[0002] 1. Field of the Invention

[0003] The methods of the present invention provide a unique and superior formulation of artesunic acid for parenteral injection and for the manufacture of the formulation under sterile conditions. The methods described herein provide a demonstrably sterile, non-pyrogenic product which dissolves rapidly with no frothing or caking, yielding a clear, conveniently prepared solution the attending physician may administer with confidence.

[0004] The formulation that is prepared by the methods of the invention is especially suitable for the treatment of severe and complicated malaria.

[0005] 2. Brief Description of Related Art

[0006] Although malaria affects about 250 million people and kills one to two million children each year, the pharmaceutical industry has shown little interest in developing new or manufacturing established antimalarial drugs not only because risks are significant, but the returns on investment are so low.

[0007] Currently, the most promising and most rapidly acting antimalarial drugs are derivatives of artemisinin (qinghaosu) obtained from qinghao or sweet wormwood (*Artemesia annua*); these drugs have been developed and manufactured in China. Three compounds of the qinghao family have been used: the parent artemisinin and two of its more-active derivatives: a water-soluble hemisuccinate, artesunate (AS), and an oil-soluble ether, artemether (AM). Both derivatives are metabolized to a common biologically active metabolite, dihydroartemisinin (DHA). Although this facile conversion (hydrolysis) to DHA contributes to the AS rapid antimalarial activity, it also limits the choices of practical AS dosage formulations.

[0008] Artesunic acid is also known to be effective in the treatment of severe (neuropathic) malaria, *Artesunate versus quinine for treatment of severe falciparum malaria; a randomized trial,* Dondorp, et al; Lancet, vol. 366, pages 717-725, Aug. 27, 2005, incorporated herein in its entirely by reference. However, Artesunic Acid is an intrinsically unstable compound, susceptible to decomposition by heat, radiation, and virtually any aqueous solution. Prior studies have confirmed the breakdown of artesunate in aqueous solutions.

[0009] AS has been used for injection with good results. However, there arc drawbacks of the current commercially available AS dosage form. It is a two-component product consisting of a dry-fill powder of sterile artesunic acid in a vial and a sterile 5% sodium bicarbonate solution in an ampoule. This product, "Artesunate For Injection", is manufactured by Guilin Pharmaceutical Factory, Guangxi, China. This presently used formulation, when dissolved in the supplied bicarbonate buffer solution, results in fizzing and incomplete solution so that the concentration (dose) to be delivered may be uncertain.

[0010] The formulation of artesunic acid mentioned above is manufactured in China, and prepared by an undivulged method which results in a product of poor dissolution characteristics, and which froths and cakes upon introduction of the dissolution medium (5% bicarbonate). As the AS dissolves, carbon dioxide is evolved and trapped in the small volume of the closed vial. The formed gas bubbles carry un-dissolved AS particles throughout the vial, thereby reducing contact between these particles and the dissolution medium and lengthening the time needed to completely dissolve the AS. Moreover, this phenomenon reduces the investigator's ability to see if the solution is complete so the next preparation step, which is to dilute the AS/bicarbonate solution with 5 mL of sterile 5% glucose solution, can begin. These delays can unduly lengthen the overall solution preparation time, resulting in a shorter time period over which the prepared solution can be administered.

[0011] Further and most importantly, the product coming from China is not manufactured under the U.S. Food and Drug Administration's current Good Manufacturing Practice (cGMP).

[0012] Therefore, it is an object of the present invention to provide an AS product and a method for preparing an AS product that dissolves quickly, thoroughly and does not cake or fizz upon dissolution.

[0013] It is another object of the present invention to prepare an AS product that does not require an additional step of diluting with glucose and is immediately usable upon dissolution.

[0014] Another object of the present invention is to develop a method for the production of an artesunic acid solution for the intravenous or intramuscular treatment of malaria that is sterile and manufactured under current Good Manufacturing Practice (cGMP) as required by the U.S. Food and Drug Administration.

[0015] Another object of the present invention is to sterilize artesunic acid powder without decomposition.

[0016] Another object of the invention is to prepare an artesunic acid product that has a shelf life of two years.

[0017] These and other objects will become apparent upon further reading of this application.

SUMMARY OF THE INVENTION

[0018] The invention is a method for the manufacture of an intravenous or intramuscular formulation of artesunic acid. First the artesunic acid powder is sterilized with ethylene oxide and placed into a sterile container. Nitrogen is used to purge water vapor from the container, after which the container is hermetically sealed. When used, the sterilized powder is dissolved in sterile sodium phosphate buffered solution to produce a solution suitable for intravenous or intramuscular administration. The sodium phosphate buffered Is solution dissolves the artesunic acid powder without caking or frothing, resulting in an improved drug product. The invention also relates to the formulation and a method of treating a patient with severe and complicated malaria.